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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Ram Pratap et al.	Group Art Unit: 1615
Serial No.: 09/742,424	Examiner: Shekih, Humeran
Filed: 22th December 2000	
For: Novel uses of guglipid: as cognitive enhancer, anti-hyperglycemic and for dermal conditions	Attorney Docket No: K&S-0100-US

To,
The Assistant Commissioner for Patents
Washington, D.C. 20231

Declaration Under 37 C.F.R. § 1.132

I, Ram Pratap age 50, residing at Central Drug Research Institute, Lucknow, INDIA, and a citizen of India, do hereby state as under.

I am a Scientist at Central Drug Research Institute (CDRI), Lucknow, INDIA. I graduated in the year 1972 from Banaras Hindu University, Varanasi (India). I completed my Master's Degree in 1974 B.H.U., INDIA in the year 1974 Subsequently, I completed my doctoral degree in 1978, Chemistry from B.H.U. After completing my doctoral degree, I took up my first assignment as a post-doctoral scientist with the BYU, USA, 1978 in Chemistry. After that, I joined the Central Drug Research Institute, Lucknow, a constituent institution of the Council of Scientific and Industrial Research, India, where I am continuing to now work on Lipid lowering agent for the last 25 years. Presently, I am working as the Scientist E-II of this institute (since 1983).

One of the projects undertaken by CDRI, Lucknow, INDIA is "*Uses of Gugulipid as cognition enhancer, antihyperglycemic and for dermal conditions*". This project was undertaken in the year 1999. The scientists involved in the study were myself, Raghwendra Pal, Satyawan Singh, Girja Shankar, Chandeshwar Nath, Hemant Kumar Singh, Deepak Raina, Arwind Kumar Srivastava, Anil Kumar Rastogi, P.S.R.Murthy, Sudhir Srivastava, Omkar Prasad Asthana, Narendra Singh and Nitya Anand. I am the main scientist (project leader) in this study. I am aware of US patent application No. 09/742,424 filed in respect of this project. I am also aware and familiar with all the office actions, objections of the Examiner and the references cited by the Examiner. Therefore, I am completely and fully aware of all the facts relating to this project as well as the present patent application.

It is very necessary to understand the nature of any disease before any medication can be invented, developed or evolved for it. In this respect, we submit that **Cognitive dysfunction is a state during which "there is a memory loss, distractibility and difficulty is multitasking"**. In fact cognitive dysfunction in common terms refers to mental incapability's wherein a person's skills like to pay attention, communication, remembrance, organizing oneself, learning, planning, understanding are very dramatically affected and impaired. Any of the above-mentioned conditions can be either short lived or prolonged, depending upon the health and age of the individual, and nature of disease. Further, when we discuss about memory loss, we mean Amnesia. **Amnesia can be symptom of many neurodegenerative problems. Thus, Amnesia can either be short lived or prolonged and again depends upon the health and age of the individual, and nature of disease.** The neurodegenerative problems may arise due to many dysfunctions like injury, physiological stress or strain, age, genetical abnormality, chemically induced physiological and biochemical changes and cancer. It is very important further to understand that **Alzheimer's disease (hereafter referred as AD) is very specific neurodegenerative disorder, which is age dependent.** AD, is a disease which is associated with impaired ability to calculate, visuospatial skills and ideomotor apraxia. We have now very explicitly defined the characteristics features of the various conditions of cognitive dysfunction as discussed in the present invention.

We also wish to further highlight that guglipid as medication for preventing cognitive dysfunction cannot be taken in isolation and does not have any dependency upon only one kind of disease or disease condition. The pharmaceutical compound, gugulipid of our invention, is a ethyl acetate extract of *Commiphora wightii.*

This fraction is gugulipid and comprises of steroids like guggulsterol-I, -II and –III. These ingredients of gugulipid may produce in the biosystem pregnenolone, which already is reported as cognition enhancing activity and is subject of our claims useful in preventing cognitive dysfunction in animals.

The flowchart clearly demonstrates that the chemical isolate gugulipid is a product of neutral fraction. This ingredient is useful in preventing cognitive dysfunction i.e. a condition that can be experienced by an individual of any age and includes people suffering from Alzheimer's disease, Schizophrenia, Amnesia, dementia, etc. It is very necessary to develop drug therapy for a disease based on the widely accepted pathology of that disease. The present invention was developed on this approach. In brief, the approach of the investigators success lies with a formulation of wide-ranging characteristics and highly effective against cognitive dysfunctions. It is not a mere chance discovery, which leads to such conclusions. The investigations are based on thoroughly analysed facts.

We have recognized the Examiner's objections of obviousness and we have addressed this objection to the obviousness earlier. Yet we submit that there is no inspiration or clue from the prior art document to seek support, and is a continuation of our own earlier studies. As claimed earlier, we had observed marked hypolipidemic activity in gugulipid, which was shown largely to be due to the presence pregnadionones, such as gugulsterones Z&E. These structures were an entirely new chemotype for hypolipidemic activity. After having demonstrated the clinical efficacy of gugulipid for hyperlipidemia, (Ref: J.Assoc Physicians India 37, 323(1989)) we naturally turned our attention to studying the mode of action of gugulipid, and found that gugulipid had antioxidant activity and

also caused inhibition cholesterol biosynthesis and increased bile acid excretion (Ref: Guggulsterone, a potent hypolipidemic, prevents oxidation of low density lipoproteins, K.Singh, R.Chander and N.K.Kapoor, *Phytotherapy Research*, II, 291 (1997))] . These studies, specially antioxidant activity focused our attention on other possible associated useful clinical activities related to antioxidant activity. One such area was the deficit in cognition, which is to a large extent due to the result of degenerative events in the central nervous system resulting from oxidative stress, and could be treated by antioxidants. Testing in this area was thus an extension of our own study and not inspired by any one else's work in this area. Rather it is other way around as Majeed et al. have taken lead from the CDRI work, which they have quoted in the prior art of Patent no US 6,436,991 B1, paragraph starting at line no 40 of first page "In the 1960's the oleogum resin (gum guggul) was studied for its potential in the treatment of elevated blood cholesterol or hyperlipidemia. This research originated from the College of Medical Sciences of Banaras Hindu University at Varanasi, India, and was continued into the 1980's at the **Central Drug Research Institute (CDRI) at Lucknow, India.** Based on the structure function analysis of gum guggul, it was determined that the soluble portion of the gum is ethyl acetate, and specifically its neutral portion, contained most of the hypolipidemic properties. The neutral fraction was found to be a source of sterol compounds known as guggulsterone Z and E (pregnane derivatives) and responsible for lowering of blood cholesterol. Subsequently, the preparation of gum guggul used by the **CDRI** in clinical studies consisted of a solid extract, standardized to contain a minimum of 2.5% of guggulsterones E and Z (Indian pharmacopea, 1988; Satyavati, 1991)".

The stimulation of plasma LCAT, hepatic lipases, receptor mediated catabolism of LDL and increased faecal bile acid excretion as well as suppression of hepatic cholesterol biosynthesis are the mechanisms responsible for lipid lowering effect of gugulipid [s. Nityananad and N.K. Kapoor, Ind. J. Exp. Biol. 11, 395 (1973); N.K. Kapoor and s. Nityanand, Ind. J. heart Res. Supp-) 22 (1988)]. If each document is looked distinctly it is observed that the compounds have different approach (our findings are on the presence of guggulsterol I,II &III antioxidant lignan and whereas Majeed's finding are based on ferulic acid ester.

Intracerebroventricular (i.c.v.) administration of pregnenolone and pregnenolone sulfate leads to an amelioration in various memory task in rodents [Flood, J. F., Morley, J. F., and Robert, E., Memory enhancing effects in male mice of pregnenolone and of steroids metabolically derived from it, *Proc. Natl. Acad. Sci.* USA, **89**, 1567 (1992)]. These memory-enhancing effects might be attributed to the N-methyl-D-aspartate (NMDA)-antagonistic properties of pregnenolone sulfate since NMDA agonists have been shown to impair cognitive functions in rodents [Bowlby, M. R., Pregnenolone sulfate potentiation of N-methyl-D-aspartate receptor channels in hippocampal neurons. *Mol. Pharmacol.*, **43**, 813 (1993)]. As already stated, cholesterol is the precursor of neurosteroid pregnenolone. These findings prompted us to explore memory enhancing properties of *gugulipid* because of similarity among biogenic precursor of pregnenolone (1) and steroids present in *Gugulipid* such as guggulsterol- I (2), guggulsterol- II (3) and guggulsterol-III (4) (Fig-1) [V. D. Patil, U.R.Nayak and Sukh Dev: Chemistry of Ayurvedic Crude Drugs –I, *Tetrahedron* **28**, 2341 (1972)]. It strongly suggests that the antidementia activity of present invention may be limited to cholesterol pregnalon hypotheses and other constituents, which are not involved in cholesterol pregnalon hypothesis such as ferulic acid may not be involved in antidementia activity of this invention. They both are individual patents with no interlinks and motivation. The present invention is more far reaching and impact creating in pharmaceutical industry.

Majeed et al. conducted the study, which is limited to only cell proliferation and anti-oxidant activities. These activities have correlation with abnormal cell growth (neoplasia) and inflammation, respectively. The role of abnormal cell growth in a neurodegenerative disorder like Alzheimer's disease has not been suggested. It is not appropriate to correlate two diverse phenomena - cell proliferation and degeneration to Alzheimer when it is regarded as neurodegenerative disease. Production of amyloid protein is not a cell proliferation process but on contrary it is being linked to neuronal degeneration. As far as inflammation is concerned, its role in Alzheimer's disease is still not established [Ref. The Lancet Neurology 2 September 2003, 544 Column 2 Second last para]. Inflammation is one out of several factors implicated in Alzheimer's disease. Clinically anti-inflammatory

drugs have failed to deliver benefits to patients. The cholinergic drugs are in front line of the drug therapy of Alzheimer's disease (Ref . Lancet). Therefore, claim of Majeed et al for Alzheimer's disease on the basis of anti-oxidant and antiproliferative is not appropriate. The animal models for anti-dementia activity are available based on cholinergic deficiency (receptor blockade or lesion in cholinergic neuronal pathway) and the drugs currently used in Alzheimer's disease were developed from these model. [1. Brioni, JD, Hock, FJ & McGaugh, J.J. (1997). Drug effects on learning and memory. In: Vogel GH and WH (eds.) Drug Discovery and Evaluation: Pharmacological Assays, Springer Verlag Press, New York, pp. 335-336. 2. Das, A.,Shanker, G., Nath, C., Pal, R., Singh S. & Singh, H.K. A comparative study of standardized extracts of *Bacopa menniera* and Ginkgo biloba in Anticholinesterase and Congritive Enhancing Activities. Pharmacol. Bicohem. Behav. 2002 (73), 893-900].

In our study, we used the anti-cholinergic model to demonstrate the potential of our product for anti-dementia disorders (Alzheimer's disease is a major dementia disorder). Thus, it is evident that our claim is based on direct experimental observation while Majeed et al., 's claim is extrapolated indirectly through those activities, which have not been accepted as established factors in Alzheimer's disease (Ref Lancet., Goodman & Gillaman...). It is amazing that a claim has been accepted for Alzheimer's disease for which no experiment was conducted though the animal models for anti-dementia activity is available. The award of claims based on clinically unestablished facts for the treatment of a disorder is improper precedence.

Infact the examiner should appreciate that the citations belonging to as old as 1972 have been cited which initially identified the functions of guggul gum. Infact the inventors will wish to highlight that the ferulic acid which has been claimed in the prior art has been well documented and isolated earlier in 1983 [Sukh Dev (1983). Chemistry of Resinous exudates of some Indian Trees. Porc. Indian Natn. Scie. Acad. 49(3), 359-385)] and thus is a not a novel molecule as claimed in prior art of Majeed *et al.*

We recognize that the Examiner objection is an objection of obviousness, and we have addressed this objection of obviousness adequately earlier. Yet, we would respectfully submit that there is no inspiration or clue from the each document to seek support for other documents or other areas of knowledge. Each document is stand-alone and there is no logical link between one document to another document. In short, both fall in different directions and the present invention provides yet another direction, which has no bearing on the citations. Whereas, the instant invention is made with a progressive approach and not with hindsight.

The Examiner must appreciate that the cited arts are of years 1972 onwards. We have put several years of research to come out with the invention of the instant application. Had it been obvious for a person skilled in the art, then, would not the much-awaited instant work come out long back? The area of invention is a very 'hot' area of research. This is so because many people suffer from cognitive dysfunctions

Had it been obvious, the invention would have taken place immediately after the cited arts. There are several research groups in various parts of the world that are active in this area of research. Had it been so obvious, they would not have waited for 12-13 years! The inventors have conducted multiple experiments of varying nature. It is only after several years of hard work involving much human involvement and inventive skills that the inventors have been able to achieve the desired results.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Ram Pratap

Ram Pratap

Dated: May 10,2004

Place: Lucknow (India)